Adoption of Adjuvant Chemotherapy for Non–Small-Cell Lung Cancer: A Population-Based Outcomes Study

Christopher M. Booth, Frances A. Shepherd, Yingwei Peng, Gail E. Darling, Gavin Li, Weidong Kong, and William J. Mackillop

ABSTRACT

Purpose

Since 2004, several clinical trials have demonstrated that adjuvant chemotherapy (ACT) improves survival in patients with early-stage non–small-cell lung cancer (NSCLC). Here, we evaluate the uptake of ACT and its impact on outcomes in the general population of Ontario, Canada.

Methods

All patients diagnosed with NSCLC in Ontario from 2001 to 2006 who underwent surgical resection ($n = 6,304$) were identified using the Ontario Cancer Registry. We linked electronic records of treatment to the registry. We described uptake of ACT and compared survival of all patients with surgically resected NSCLC diagnosed from 2001 to 2003 with patients diagnosed from 2004 to 2006. As a proxy measure of ACT-related toxicity, we evaluated hospitalizations within 6 months of surgery.

Results

Demographic, disease, and treatment-related characteristics did not differ between the 2001 to 2003 and 2004 to 2006 study cohorts. Over the study period, the proportion of patients receiving ACT increased from 7% (192 of 2,950 patients) to 31% (1,032 of 3,354 patients; $P < .001$). The proportion of patients admitted to hospital within 6 months of surgery remained stable and (36% in the 2001 to 2003 cohort and 37% in the 2004 to 2006 cohort). However, within 2 years of surgery, there was a 33% reduction in the proportion of patients admitted to hospital with metastatic disease ($P < .001$). During the study period, there was a substantial improvement in 4-year survival among surgically resected patients, from 52.5% (2001 to 2003) to 56.1% (2004 to 2006; $P = .001$).

Conclusion

There has been a rapid uptake of ACT for NSCLC, which was not associated with an increased rate of hospitalization. The adoption of ACT was associated with a substantial improvement in overall survival, suggesting that the benefits seen in clinical trials are generalizable to the general population.

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INTRODUCTION

Lung cancer is the leading cause of cancer mortality in the Western world and accounts for more deaths than breast, colon, and prostate cancers combined.¹ Surgical resection remains the treatment of choice for stage I and II and some stage IIIa non–small-cell lung cancer (NSCLC). Despite improvements in surgical technique, 5-year survival rates for stage I and II NSCLC are only 60% to 70% and 35% to 40%, respectively.² On the basis of the results of four large randomized controlled trials (RCTs) published since 2004, adjuvant cisplatin-based chemotherapy has become recommended for early-stage NSCLC.³ It is not known to what extent adjuvant chemotherapy (ACT) for NSCLC has been adopted

and whether the net benefits seen in RCTs translate into comparable results in the general population.

Population-level databases allow investigators to evaluate uptake, safety, and outcomes of novel medical therapies in the real world.^{4,5} Contemporary population-based outcome studies may provide insight into practice patterns, the impact of a change in practice and/or policy on outcomes, whether serious toxicities emerge outside the clinical trial environment, the economic impact of new medical therapies, and the societal benefit of medical research. For these reasons, population-based outcome studies are becoming increasingly recognized as important in the generation and dissemination of medical evidence and are one of the cornerstones of comparative-effectiveness research.^{4,6} Such natural

From the Queen's University Cancer Research Institute; Institute for Clinical Evaluative Sciences, Queen's Health Services Research Facility, Kingston; Princess Margaret Hospital; and Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada.

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Corresponding author: Christopher M. Booth, FRCP, Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, 10 Stuart St, Kingston, Ontario, K7L 3N6, Canada; e-mail: boothc@kgh.kari.net.

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experiments have been used effectively by many groups to assess the impact of shifts in practice on outcomes at the population level.^{4,7-9} We undertook this population-based cohort study to evaluate uptake of ACT for NSCLC and to assess its impact on outcomes at the population level.

METHODS

Study Design and Population

This population-based, retrospective cohort study compared the management and outcome of early-stage NSCLC in the Canadian province of Ontario before and after 2004. Ontario has a population of approximately 11.4 million people and a single-payer universal health insurance program. All patients diagnosed with NSCLC in Ontario from 2001 to 2006 who underwent surgical resection within 24 weeks of diagnosis were included. Because convincing data for ACT in NSCLC were first published in 2004, our study population was divided into preadoption (diagnosis from 2001 to 2003) and postadoption cohorts (diagnosis from 2004 to 2006). Patients treated with preoperative radiotherapy and/or neoadjuvant chemotherapy (both defined as treatment given between dates of diagnosis and surgery) were excluded.

Data Sources

The Ontario Cancer Registry (OCR) is a passive, population-based cancer registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer diagnosed in the province of Ontario.^{3,10,11} The OCR provided the following information: International Classification of Diseases, version 9 code; the International Classification of Diseases for Oncology histology code; age, sex, and place of residence; and date of death. Complete information about vital status was available up to October 2008. The OCR does not compile information about extent of disease or treatment. Indicators of the socioeconomic status of the community in which patients resided at time of diagnosis were linked to the OCR, as described previously.¹²

A variety of electronic administrative health databases were linked to the OCR. Records of hospitalization from the Canadian Institute for Health Information provided information about surgical interventions, physician providers, and hospital care. Hospital participation in collection of separation records is known to be consistent and complete throughout Ontario.¹³ Physicians in Ontario submit billing codes for chemotherapy to the Ontario Health Insurance Plan for remuneration. Physician billing codes for chemotherapy from the Ontario Health Insurance Plan database were linked to the study database, allowing us to identify which patients received chemotherapy (but not the drug/regimen name) and the date of treatment for all patients in the province. The clinical databases of Ontario's Regional Cancer Centers (RCCs) and Princess Margaret Hospital (PMH) provided detailed records of chemotherapy (including drug and dose) and radiotherapy delivery. Most chemotherapy records at RCC/PMH were captured automatically at the point of prescription through the centers' information systems and were, therefore, of high quality. Because a substantial proportion of chemotherapy (approximately 50%) is delivered by medical oncologists who are not associated with RCC/PMH, chemotherapy physician billing codes (as described earlier) were used to describe, in general terms, the use of ACT among all patients in Ontario. RCC/PMH centers are the only providers of radiotherapy in the province, and the electronic radiotherapy records are known to be 95% complete and 99% accurate.¹⁴ Stage of disease at diagnosis is only captured routinely for patients seen at RCCs. The study was approved by the Research Ethics Board of Queen's University.

Definitions of Comorbidity, Management, and Outcomes

Comorbidity was classified using the Charlson Index modified for administrative data based on all noncancer diagnoses recorded on any hospital admission within 5 years before surgery.^{15,16} Surgical resection was defined as pneumonectomy, lobectomy, or segmentectomy. To minimize error as a result of miscoding of surgical procedures, a minimum length of stay was set at 3 days. Patients who died within this period remained in the study population to account for early postoperative deaths. Adjuvant therapy was defined as any

chemotherapy or radiotherapy administered within 16 weeks after surgery. We used the Canadian Institute for Health Information database to compare frequency and duration of hospitalizations within 6, 12, and 24 months of surgery to explore treatment- and disease-related toxicities. The primary end point for outcome assessment was 4-year survival.

Statistical Analysis

Characteristics of the pre- and postadoption cohorts were compared using the χ^2 test. The primary study objective was to compare 4-year survival between the 2001 to 2003 and 2004 to 2006 cohorts. Overall survival was determined from date of diagnosis using the Kaplan-Meier method, and comparisons between groups were made using the log-rank test. Factors associated with use of ACT were evaluated by logistic regression. Variables with $P < .1$ in univariate analysis were entered into the multivariate analysis. A stepwise selection technique was used with a significance level for entry and exit of $P = .1$. Predictors were considered statistically significant at $P < .05$. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Table 1. Demographics and Clinical Characteristics of Patients Diagnosed With Non-Small-Cell Lung Cancer in Ontario From 2001 to 2006 Who Underwent Surgical Resection

Characteristic	2001-2003 (n = 2,950)		2004-2006 (n = 3,354)	
	No. of Patients	%	No. of Patients	%
Age, years				
20-49	163	6	180	5
50-59	547	19	601	18
60-69	1,000	34	1,078	32
70-79	1,060	36	1,225	37
80+	180	6	270	8
Male sex	1,601	54	1,718	51
Socioeconomic status by quintile				
1	665	23	717	21
2	736	25	783	23
3	619	21	718	21
4	513	18	603	18
5	405	14	529	16
Charlson comorbidity score				
0	2,099	71	2,460	73
1-2	740	25	764	23
3+	111	4	130	4
Histology				
Adenocarcinoma	1,646	56	1,830	55
Squamous carcinoma	980	33	1,018	30
Large-cell carcinoma	64	2	72	2
Mixed	54	2	102	3
Carcinoma NOS	206	7	332	10
Pathologic stage				
I	235	8	581	17
II	157	5	281	8
III	152	5	215	6
IV	78	3	128	4
Unknown	2,328	79	2,149	64
Surgery				
Pneumonectomy	422	14	398	12
Lobectomy	1,727	59	2,007	60
Segmentectomy	801	27	949	28
Median LOS after surgery, days	7		7	
Referral to regional cancer center	1,361	46	1,820	54
Postoperative radiotherapy	314	11	322	10

NOTE. Percentages may not add to 100% because of rounding. Abbreviations: NOS, not otherwise specified; LOS, length of stay.

RESULTS

Patients

During 2001 to 2006, there were 28,862 patients diagnosed with NSCLC in Ontario, of whom 6,570 underwent surgical resection; 266 patients (4%) were treated with preoperative radiotherapy and/or neoadjuvant chemotherapy and were thus excluded from this study. The final study population included 6,304 surgically resected patients; characteristics are listed in Table 1. The proportion of all patients who underwent surgical resection did not differ between study periods (22% [2,950 of 13,678 patients] in 2001 to 2003 and 22% [3,354 of 15,184 patients] in 2004 to 2006). There were no substantial differences in important prognostic variables between the two study cohorts. TNM stage is captured routinely only for patients seen at RCCs. The apparent difference in stage distribution between the time periods may be explained by the increased number of patients with early-stage disease referred to RCCs for consideration of adjuvant therapy after 2004. Concomitant with the increase in the number of patients referred to an RCC (46% to 54%; $P < .001$), there was a proportional decrease in patients with unknown stage and a parallel increase in patients with stage I or II disease with no meaningful change in the proportion of patients with stage III or IV disease.

Adoption of ACT

Use of ACT was identified in 1,224 patients among the complete study population (2001 to 2006; Fig 1). Among the 676 patients identified as being treated with ACT at RCC/PMH, we identified corresponding physician billing records for ACT in 645 patients (95%), suggesting that billing records for chemotherapy are complete.

Temporal trends in the adoption of ACT are shown in Figure 2. During the study period, the proportion of patients who received ACT increased from 7% (192 of 2,950 patients) in 2001 to 2003 to 31% (1,032 of 3,358 patients) in 2004 to 2006 ($P < .001$). Drug and regimen information were available for 584 of the 597 patients in the postadoption cohort treated at RCC/PMH. Among these patients, 82% received cisplatin-based therapy, and 17% received carboplatin.

Patterns of ACT use in 2004 to 2006 are listed in Table 2. Approximately 64% of patients with resected stage II or III disease were treated with ACT. Although 56% of patients younger than 50 years old were

Fig 2. Proportion of patients with surgically resected non-small-cell lung cancer diagnosed in Ontario (N = 6,304) from 2001 to 2006 who received adjuvant chemotherapy. Pivotal randomized controlled trials were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2003 (International Adjuvant Lung Cancer Trial), 2004 (JBR.10 and Cancer and Leukemia Group B [CALGB] trials), 2005 (Adjuvant Navelbine International Trialist Association trial), and 2006 (updated CALGB trial).

treated with ACT, only 16% of patients older than age 70 years were treated. In the logistic regression, we found that patients with younger age, less comorbidity, shorter length of surgical stay in hospital, more extensive surgery, and stage II or III disease were more likely to receive ACT. We also observed wide variations in utilization of ACT across geographic regions of Ontario; ACT use among surgically resected patients ranged from 22% to 44% across the province.

Outcomes

As shown in Figure 3, we found that the proportion of patients undergoing surgical resection decreased considerably during the 1990s before stabilizing in 2001 to 2006 (22% in 2001 to 2003 and 2004 to 2006). During the same time period, we observed a substantial increase in the proportion of patients undergoing computed tomography (CT) within 6 months of diagnosis, suggesting that surgical patient selection may have improved over this time period. Use of CT imaging did not change appreciably during 2001 to 2006 (overall rate: 95% in 2001 to 2003 and 97% in 2004 to 2006). During the study period, positron emission tomography was not widely available in Ontario except on clinical trials.¹⁷

Figure 4 illustrates temporal trends in overall survival for all patients with NSCLC in Ontario. During the study period, 4-year survival for surgically resected patients (Fig 4A) improved from 52.5% in 2001 to 2003 to 56.1% in 2004 to 2006 ($P = .001$). Among all study patients (Fig 4B), survival at 4 years was 18.4% for 2001 to 2003 and 19.0% for 2004 to 2006 ($P = .297$). We also evaluated trends in survival before 2001 (Figs 4C and 4D). Corresponding to the change in surgically resected patient selection and the uptake of CT imaging, we found that survival of surgically resected patients improved from 1992 to 1995 to 1996 to 2000 (4-year survival rate: 46.9% to 51.0%, respectively; $P < .001$) before stabilizing during the subsequent period (4-year survival rate: 1996 to 2000, 51.0%; 2001 to 2004, 52.5%; $P = .575$).

As a proxy measure of major treatment-related toxicity, we evaluated admissions to hospital within 6 months. The proportion of patients admitted to hospital did not change appreciably between

Fig 1. Identification of patients administered adjuvant chemotherapy (ACT) among all patients with surgically resected non-small-cell lung cancer diagnosed in Ontario from 2001 to 2006 (N = 6,304). OHIP, Ontario Health Insurance Plan; RCC, Regional Cancer Center; PMH, Princess Margaret Hospital.

Table 2. Variables Associated With Use of ACT Among 3,354 Surgical Patients With Non–Small-Cell Lung Cancer in Ontario From 2004 to 2006

Variable	Total No. of Patients	% of Patients With ACT	Univariate Analysis			Multivariable Analysis		
			OR	95% CI	P	OR	95% CI	P
Sex								
Male	1,718	30	Ref					
Female	1,636	32	1.1	0.9 to 1.3	.308			
Age, years								
20-49	180	56	6.5	4.7 to 9.0	< .001	5.8	4.1 to 8.2	< .001
50-59	601	49	4.9	4.0 to 6.1	< .001	4.7	3.7 to 5.9	< .001
60-69	1,078	37	3.1	2.6 to 3.7	< .001	2.9	2.4 to 3.6	< .001
70+	1,495	16	Ref			Ref		
Socioeconomic status, quintile								
1	717	29	Ref			Ref		
2	783	35	1.4	1.1 to 1.7	.007	1.4	1.1 to 1.8	.007
3	718	30	1.1	0.8 to 1.3	.654	1.0	0.8 to 1.3	.972
4	603	29	1.0	0.8 to 1.3	.769	1.0	0.7 to 1.3	.888
5	529	31	1.1	0.9 to 1.4	.330	1.0	0.7 to 1.3	.896
Charlson comorbidity score								
0	2,460	33	2.9	1.8 to 4.8	< .001	2.2	1.3 to 3.7	.005
1-2	764	25	2.0	1.2 to 3.3	.010	1.9	1.1 to 3.2	.031
3+	130	15	Ref			Ref		
Histology								
Adenocarcinoma	1,830	31	Ref					
Squamous carcinoma	1,018	29	0.9	0.8 to 1.1	.497			
Large-cell carcinoma	72	32	1.1	0.6 to 1.8	.793			
Mixed	102	36	1.3	0.9 to 2.0	.219			
Carcinoma NOS	332	35	1.2	1.0 to 1.6	.108			
Pathologic stage								
I	581	36	Ref			Ref		
II	281	66	3.4	2.5 to 4.6	< .001	3.7	2.7 to 5.1	< .001
III	215	61	2.8	2.0 to 3.8	< .001	2.8	2.0 to 4.0	< .001
IV	128	38	1.1	0.7 to 1.6	.745	0.9	0.6 to 1.4	.601
Unknown	2,149	21	0.5	0.4 to 0.6	< .001	0.5	0.4 to 0.6	< .001
Surgery								
Pneumonectomy	398	47	2.5	2.0 to 3.3	< .001	2.1	1.6 to 2.8	< .001
Lobectomy	2,007	30	1.2	1.0 to 1.5	.022	1.2	1.0 to 1.5	.029
Segmentectomy	949	26	Ref			Ref		
Length of hospital stay								
< Median	1,648	35	1.4	1.2 to 1.7	< .001	1.3	1.1 to 1.5	.008
≥ Median	1,706	27	Ref			Ref		
Geographic region of Ontario								
A	1,386	30	Ref			Ref		
B	502	22	0.7	0.5 to 0.9	.001	0.5	0.4 to 0.6	< .001
C	291	38	1.4	1.1 to 1.8	.011	0.8	0.6 to 1.1	.193
D	335	28	0.9	0.7 to 1.2	.586	0.5	0.4 to 0.7	< .001
E	73	44	1.8	1.1 to 3.0	.013	1.1	0.6 to 1.8	.802
F	106	35	1.3	0.8 to 1.9	.277	0.7	0.4 to 1.1	.144
G	207	37	1.4	1.0 to 1.8	.047	0.9	0.6 to 1.3	.613
H	452	35	1.3	1.0 to 1.6	.053	0.9	0.7 to 1.1	.227

Abbreviations: ACT, adjuvant chemotherapy; OR, odds ratio; Ref, reference group; NOS, not otherwise specified.

2001 to 2003 and 2004 to 2006 (36% v 37%, respectively); hospitalization rates among surviving patients also remained unchanged at 6 to 12 months (34% v 33%, respectively) and 12 to 24 months (50% v 50%, respectively) after surgery. However, within 24 months of surgery, there was a 33% reduction in the proportion of patients admitted to hospital with metastatic disease ($P < .001$).

DISCUSSION

Translation of knowledge from RCTs into societal benefit requires that the novel therapy is adopted by practitioners without an unex-

pected increase in toxicity and that patients in the general population derive the same benefits seen in clinical trials. In this large population-based study, we have explored practice patterns and outcomes among patients with resected NSCLC. Several important findings have emerged. First, we have observed rapid adoption of ACT since publication of pivotal RCTs in 2004, and the drugs used are those for which there is the strongest clinical trial evidence. However, despite the rapid uptake of knowledge, ACT may be underused in the general population. Second, the uptake of ACT does not seem to be associated with any increase in major chemotherapy-related toxicity as measured by rates of hospitalization in the first 6 months after surgery. In fact,

Fig 3. Proportion of all patients with non-small-cell lung cancer (NSCLC) diagnosed in Ontario from 1992 to 2006 (N = 65,486) who underwent surgical resection and proportion of patients who underwent computed tomography (CT) within 6 months of diagnosis.

among patients with resected NSCLC, the number of admissions to hospital for metastatic disease decreased considerably between 2001 and 2003 and 2004 to 2006. Third, we have found a substantial improvement in survival among patients with resected NSCLC at the popula-

tion level consistent with the relevant clinical trials. Finally, this study demonstrates how comparative-effectiveness research may evaluate the use and benefits of new medical therapies in the real world.

The role of ACT for NSCLC has been established based on several RCTs published since 2004.³ The International Adjuvant Lung Cancer Trial found that cisplatin-based ACT was associated with a 4% absolute improvement in survival at 5 years compared with observation alone.¹⁸ Adjuvant vinorelbine/cisplatin led to improved outcomes in both the National Cancer Institute of Canada Clinical Trials Group and North American Intergroup study JBR.10 and the Adjuvant Navelbine International Trialist Association (ANITA) trial, with absolute improvements in survival of 15% and 9% at 5 years, respectively.^{19,20} Finally, the Cancer and Leukemia Group B 9633 trial evaluated paclitaxel and carboplatin in patients with stage IB disease. Although initial results presented in 2004²¹ showed a 12% absolute improvement in survival at 4 years, when mature data were presented in 2006, the difference was no longer statistically significant.^{22,23} The results of these individual RCTs and a recent meta-analysis have changed practice and led to international bodies now recommending cisplatin-based ACT for patients who have undergone resection of NSCLC.^{24,25}

Since 2004, there have been three published reports evaluating the uptake of ACT for NSCLC.²⁶⁻²⁸ Although these reports describe a relatively small number of surgically resected patients (n = 108, n = 204, and n = 219), all studies found a significant increase in the use of

Fig 4. Survival curves for (A) patients with non-small-cell lung cancer (NSCLC) in Ontario diagnosed from 2001 to 2006 who underwent surgical resection, (B) all patients with NSCLC diagnosed from 2001 to 2006, (C) all patients with NSCLC who underwent surgical resection from 1992 to 2006, and (D) all patients with NSCLC in Ontario diagnosed from 1992 to 2006.

ACT after 2004. Small sample sizes precluded any evaluation of toxicity and survival.

Although, to our knowledge, our study is the first comprehensive study to date that has evaluated uptake and outcomes of ACT in NSCLC, several methodologic limitations merit comment. Although the data sources used in this study describe general aspects of disease, treatment, and outcome for all patients in Ontario, detailed information related to chemotherapy administration, treatment toxicity, performance status, and stage of disease is not available for all patients. This limits our ability to evaluate the appropriateness of patient selection for ACT. It is possible that other unmeasured variables changed during 2001 to 2006 that may have influenced the observed improvement in survival. The most important of these variables might be stage migration as a result of the improved sensitivity of radiologic imaging techniques. Indeed, we did see changes in the proportion of patients undergoing surgical resection in the 1990s, which we attribute to the introduction and widespread availability of CT scanning. Radiologic staging did not change in Ontario between 2001 and 2006. Of greatest importance in this regard, positron emission tomography was not available outside a clinical trial during the entire time period of our study.¹⁷ Finally, we have explored rates of hospitalization as a surrogate for the most serious toxicity related to ACT. Trends in rates of hospitalization may be confounded by changes of practice regarding inpatient care and greater use of community resources. Furthermore, specific diagnoses associated with hospitalizations may be prone to misclassification bias.

In addition to its large sample size and resulting statistical power, a major strength of the current study is the fact that, by virtue of the OCR, our study population includes all patients with NSCLC within Ontario and is thus unselected. By including the entire population of interest, it is possible to minimize the referral and selection biases that plague traditional institution-based observational studies.⁴ Furthermore, the well-defined temporal differences in practice allowed us to use a before-and-after approach to minimize error by confounding. Within most clinical contexts, when there is an abrupt change in treatment practice, it is likely that these assumptions hold true, and any difference in outcome usually can be attributed to the uptake of the novel therapy in question. Given the relatively short temporal period under consideration in this study and the fact that other important characteristics remained stable during 2001 to 2006, we feel it is unlikely that major imbalances in performance status or stage of disease exist between the two study cohorts, although full data could not be captured for these two important prognostic variables. The technique of grouping patients with a variable that is a marker for different practice policies (usually temporal period or geographic region), but is not directly associated with treatment selection or outcome, originated in econometrics and is now recognized within outcomes research as the instrumental variables approach.^{29,30}

The utilization rate of approximately 31% for all surgically resected patients in 2004 to 2006 is likely an underestimate because the existing data sources do not clearly identify which patients would be ineligible for ACT based on comorbidity and other disease-related characteristics including stage of disease. Despite this, the wide variation in ACT use across age groups and regions of Ontario suggests there may be underutilization of this therapy in the general population. Although data from RCTs suggest that the benefit of ACT for NSCLC is not age dependent,^{31,32} our results suggest that therapy may be underused among elderly patients. The rate of ACT utilization

appeared to peak in 2005 before decreasing in 2006. This potentially may be explained by a decrease in the proportion of patients with stage I tumors who received ACT after the negative updated results of the Cancer and Leukemia Group B 9633 trial presented in 2006.^{21,22} Furthermore, subset analyses of both JBR.10 and ANITA showed no significant benefit from ACT in patients with small stage IB tumors.^{19,20}

It is of interest to note that the observed absolute improvement in overall survival seen in JBR.10 and ANITA (15% and 9% at 5 years, respectively) is consistent with the 4% absolute improvement at 4 years in our own study when one considers that only approximately 31% of patients in 2004 to 2006 received ACT. In fact, the 4-year overall survival rate for patients in 2004 to 2006 who were administered ACT was 57%, which is comparable to the results of the relevant trials.^{19,20} Furthermore, considering that approximately 22% of all patients with NSCLC underwent surgical resection, the improvement in survival seen in the surgical population (3.6%) is consistent with the observed 0.6% improvement in survival of all patients with NSCLC in the general population. Although these comparative figures are helpful for illustrative purposes, more precise estimates of the survival benefit of ACT in the general population would require information on stage of disease for all patients.

In an effort to improve translation of evidence into practice, efforts should be undertaken to identify factors associated with potential underuse (and/or overuse) of new medical therapies. Educational initiatives within Ontario are planned to improve and explore appropriate utilization of ACT for NSCLC based on factors identified in this study.

In summary, this population-based study has found substantial adoption of ACT for NSCLC since 2004 and that ACT is not associated with an increased rate of toxicity leading to postoperative hospitalization. The use of ACT is associated with a substantial improvement in survival, suggesting that the benefits seen in the relevant clinical trials are generalizable to the general population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Christopher M. Booth, Frances A. Shepherd, Yingwei Peng, Gail E. Darling, Gavin Li, Weidong Kong, William J. Mackillop

Financial support: Christopher M. Booth, William J. Mackillop

Administrative support: Christopher M. Booth, William J. Mackillop

Provision of study materials or patients: Christopher M. Booth, William J. Mackillop

Collection and assembly of data: Christopher M. Booth, Frances A. Shepherd, Yingwei Peng, Gail E. Darling, Gavin Li, Weidong Kong, William J. Mackillop

Data analysis and interpretation: Christopher M. Booth, Frances A. Shepherd, Yingwei Peng, Gail E. Darling, Gavin Li, Weidong Kong, William J. Mackillop

Manuscript writing: Christopher M. Booth, Frances A. Shepherd, Yingwei Peng, Gail E. Darling, William J. Mackillop

Final approval of manuscript: Christopher M. Booth, Frances A. Shepherd, Yingwei Peng, Gail E. Darling, Gavin Li, Weidong Kong, William J. Mackillop

REFERENCES

1. American Cancer Society: Cancer Facts and Figures 2008. Atlanta, GA, American Cancer Society, 2008
2. Mountain CF: Revisions in the International System for Staging Lung Cancer. *Chest* 111:1710-1717, 1997
3. Booth CM, Shepherd FA: Adjuvant chemotherapy for resected non-small cell lung cancer. *J Thorac Oncol* 1:180-187, 2006
4. Booth CM, Mackillop WJ: Translating new medical therapies into societal benefit: The role of population-based outcome studies. *JAMA* 300:2177-2179, 2008
5. Wen SW, Kramer MS: Uses of ecologic studies in the assessment of intended treatment effects. *J Clin Epidemiol* 52:7-12, 1999
6. Conway PH, Clancy C: Comparative-effectiveness research: Implications of the Federal Coordinating Council's report. *N Engl J Med* 361:328-330, 2009
7. Stiell IG, Wells GA, Field BJ, et al: Improved out-of-hospital cardiac arrest survival through the inexpensive optimization of an existing defibrillation program: OPALS study phase II. Ontario Prehospital Advanced Life Support. *JAMA* 281:1175-1181, 1999
8. Pearcey R, Miao Q, Kong W, et al: Impact of adoption of chemoradiotherapy on the outcome of cervical cancer in Ontario: Results of a population-based cohort study. *J Clin Oncol* 25:2383-2388, 2007
9. Rothwell PM, Giles MF, Chandratheva A, et al: Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): A prospective population-based sequential comparison. *Lancet* 370:1432-1442, 2007
10. Robles SC, Marrett LD, Clarke EA, et al: An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol* 41:495-501, 1988
11. Clarke EA, Marrett LD, Krieger N: Cancer registration in Ontario: A computer approach, in Jensen OM, Parkin DM, MacLennan R (eds): *Cancer Registration Principles and Methods*. Lyon, France, International Agency for Research on Cancer, 1991, pp 246-257
12. Mackillop WJ, Zhang-Salomons J, Groome PA, et al: Socioeconomic status and cancer survival in Ontario. *J Clin Oncol* 15:1680-1689, 1997
13. Williams J, Young W: A summary of studies on the quality of health care administrative databases in Canada, in Goel V, Williams JI, Anderson GM, et al (eds): *Patterns of Health Care in Ontario: The ICES Practice Atlas*. Ottawa, Ontario, Canada, Canadian Medical Association, 1996, pp 339-345
14. Mackillop WJ, Fu H, Quirt CF, et al: Waiting for radiotherapy in Ontario. *Int J Radiat Oncol Biol Phys* 30:221-228, 1994
15. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 40:373-383, 1987
16. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 45:613-619, 1992
17. Evans WK, Laupacis A, Gulenchyn KY, et al: Evidence-based approach to the introduction of positron emission tomography in Ontario, Canada. *J Clin Oncol* 27:5607-5613, 2009
18. Arriagada R, Bergman B, Dunant A, et al: Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 350:351-360, 2004
19. Winton T, Livingston R, Johnson D, et al: Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 352:2589-2597, 2005
20. Douillard JY, Rosell R, De Lena M, et al: Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A randomised controlled trial. *Lancet Oncol* 7:719-727, 2006
21. Strauss GM, Herdon MA, Maddaus DM, et al: Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633. *J Clin Oncol* 22:621s, 2004 (suppl 14S; abstr 7019)
22. Strauss GM, Herdon JE, Maddaus MA, et al: Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): Update of Cancer and Leukemia Group B (CALGB) protocol 9633. *J Clin Oncol* 24:365s, 2006 (suppl 18S; abstr 7007)
23. Strauss GM, Herndon JE 2nd, Maddaus MA, et al: Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 26:5043-5051, 2008
24. Alam N, Darling G, Evans WK, et al: Adjuvant chemotherapy for completely resected non-small cell lung cancer: A systematic review. *Crit Rev Oncol Hematol* 58:146-155, 2006
25. Pisters KM, Evans WK, Azzoli CG, et al: Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIa resectable non small-cell lung cancer guideline. *J Clin Oncol* 25:5506-5518, 2007
26. Kassam F, Shepherd FA, Johnston M, et al: Referral patterns for adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. *J Thorac Oncol* 2:39-43, 2007
27. Younis T, Al-Fayea T, Virik K, et al: Adjuvant chemotherapy uptake in non-small cell lung cancer. *J Thorac Oncol* 3:1272-1278, 2008
28. Massard C, Tran Ba Loc P, Haddad V, et al: Use of adjuvant chemotherapy in non-small cell lung cancer in routine practice. *J Thorac Oncol* 4:1504-1510, 2009
29. Groome PA, Mackillop WJ: Uses of ecologic studies in the assessment of intended treatment effects. *J Clin Epidemiol* 52:903-904, 1999
30. Earle CC, Tsai JS, Gelber RD, et al: Effectiveness of chemotherapy for advanced lung cancer in the elderly: Instrumental variable and propensity analysis. *J Clin Oncol* 19:1064-1070, 2001
31. Pepe C, Hasan B, Winton TL, et al: Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. *J Clin Oncol* 25:1553-1561, 2007
32. Früh M, Rolland E, Pignon JP, et al: Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer. *J Clin Oncol* 26:3573-3581, 2008